

Stem cells and mechanisms contributing to human cortical malformations, (STEM-MCD)

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The brain and especially the cerebral cortex, have greatly expanded during evolution. Human brain development and architecture are complex, since the brain is extensively folded and contains many more cells than the rodent brain. There is a difficulty interpreting what goes wrong in human cortical malformations, which are quite severe and associated with intellectual disability as well as epilepsy. Modeling in the mouse can reveal certain defects although mouse brains lack abundant cell types critical for human brain development. Such cells play an important role during proliferation, amplifying and organizing neurons. In order to help study such processes and the variability of certain cortical malformations it is useful to work with cells derived from patients which are reprogrammed to reproduce human brain development in cell culture. In this project, as well as using mouse models and human fetal brain sections, we will compare different patient cortical progenitor cell cultures reprogrammed from fibroblasts, searching for defects during cell proliferation as well as in neuronal cells. Using state-of-the-art microscopy techniques we will visualize cell abnormalities. We will also assess global gene expression in order to help explain molecular mechanisms. Identifying molecular and cellular defects will allow us to focus on subcellular processes which are perturbed, in order to search for corrective strategies.